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Linjär blockpolymer

**TEKNISKT OMRÅDE**

- 5 Uppfinningen avser en linjär blockpolymer, och olika beredningsformer framställda av den linjära blockpolymeren samt ett implantat innefattande den linjära blockpolymeren.

**TEKNIKENS STANDPUNKT**

10

Vid vissa skador på mjukdelar i kroppen förmår kroppen ej att läka ihop dessa skador. Ett exempel på sådan skador är meniskskador, vilka har varit vanligt hos vissa idrottsutövare. Vid sådana skador brukade den skadade delen avlägsnas, med sämre kroppsfunction som följd och för en elitidrottare innebar det ofta slutet på karriären. En fortsatt stor belastning på ett knä saknande menisk leder till skelettnedsättning på mötande ytor, med ständiga smärtor som sannolik följd.

15

- En annan vävnad som är förknippad med idrottsskador är knäets korsband.
- 20 Dessa ligament stabiliserar knät. Vid skador på korsbanden är fortsatt idrottsutövning inom vissa sporter förenat med högre risker för skador på skelettdelar.

25

Redan på 1960-talet började försök göras med att ersätta skadade ligament med konstgjorda, implantat. De material som användes för de konstgjorda ligamenten var till exempel polytetrafluoreten, polyetentereftalat, polypropen, polyeten och kolfibrer.

30

Tyvärr uppvisade dessa tidiga implantat en del rad nackdelar. Det uppstod bland annat irreversibel förlängning och brott på implantaten. Den elastiska modulen för de ovan angivna materialen är för hög för att materialen skulle

kunna fungera bra i implantat som är en ersättning för till exempel knäets korsband.

- Vidare var det önskvärt att materialet i implantat var biokompatibla och
- 5 nedbrytbara i den bemärkelsen att det befrämjade tillväxten hos den skadade vävnaden och samtidigt själv bröts ner så att den skadade vävnaden återbildades och tog över funktionen allt eftersom implantatet bröts ned. Ovanstående material uppvisade ej dessa egenskaper.
- 10 I SE, 505 703, C2 beskrivs ett material som är blokompatibelt och nedbrytbart för användning i implantat. Det material som beskrivs är en linjär blockpolymer innefattande urea- och uretangrupper vilken polymer uppvisar en molekylvikt som är minst  $10^4$  Dalton.
- 15 Under det att implantat innefattande detta material har fungerat tillfredsställande, är det dock många biologiska och mekaniska parametrar som skall uppfyllas av ett material som används i ett bionedbrytbart implantat.
- 20 Hög initial styrka hos implantatet erfordras för att förhindra brott på det innan den egna vävnaden återskapats och tagit över funktionen. En gradvis nedbrytning hos materialet är nödvändig för att inducera återbildning av den egna vävnaden. Nedbrytningshastigheten bör balanseras för att få optimal återbildning av den egna vävnaden. De mekaniska egenskaperna skall vara
- 25 motsvarande de för den naturliga vävnaden, så normal funktion kan uppnås under inläkning.
- Det finns således fortfarande ett behov att optimera de mekaniska egenskaperna och nedbrytningshastigheten hos ett material avsett att
- 30 Innefattas i ett implantat.

07-06-70

Huyudfexan Kassan



25 varvid de monomerer som R1 och R2 är härledda från tillsätts i sådana mängder att molförhållandet mellan R1 och R2 är större än 2:1. Det vill säga mängden mol tillsatt monomer som R1 härleds ifrån är mer än två gånger så stort som mängden mol tillsatt monomer som R2 härleds ifrån. Såsom beskrivs nedan i exemplen tillsätts således mer än dubbelt så mycket isocyanat som esterdiol till polymerisationskärl.

Genom uppfinningen fås en polymer som är mer optimerad vad beträffar de mekaniska egenskaper och nedbrytningsegenskaper hos polymeren. Det material som kan framställas av polymeren kan göras styvare. Det får också en lägre nedbrytningshastighet. Det vill säga de styrkan hos materialet avtar

5 långsammare än för konventionella resultat. Hur fort nedbrytningen går beror på vilka monomerer som används som utgångsmaterial.

Enligt en utföringsform av uppfinningen är R1 härledd från någon av följande: etylendiamin, 1,3- diaminopropan, 1,2- diaminopropan, 1,4-

10 diaminobutan, 1,5- diaminopentan, eller 1,6 -diaminohexan.

Enligt en utföringsform av uppfinningen är R3 härledd från någon av följande dioler: polykaprolaktondiol, polydietylglykoladipat, eller poly(pentandiolpimelat).

15

Enligt uppfinningen kan den linjära blockpolymeren spinnas till en fiber. Dessa fibrer kan spinnas till exempel genom en våtspinningsprocess beskriven i "Gisselfält, K.; Flodin, P. Macromol. Symp. 1998, 130, 103-11".

20 Företrädesvis uppvisar fibrerna framställda av den linjär blockpolymer enligt ovan en specifik styrka på åtminstone 0.1 N/tex, gärna överstigande 0.2 N/tex. Genom att fibrerna dessutom uppvisar hög styvhet, kan ett implantat framställt av fibrerna erhålla en styvhet som gör att implantatet fungerar väl som ersättning för den egna vävnaden. För att vissa implantat skall fungera

25 väl i kroppen bör inte brottöjningen vara alltför hög, vilket ofta är fallet med andra polyuretanfibrer av Spandextyp, t.ex. Lycra. En fiber framställd av den linjära blockpolymeren enligt uppfinningen uppvisar företrädesvis en brottöjning som understiger 100 %.

30 Den linjära blockpolymeren kan användas i olika beredningsformer, beroende på vilken användning som åsyftas. Exempel på beredningsformer är fiberform, skumform och filmform.

Ytterligare exempel på beredningsformer är porösa filmer eller porösa polymermaterial.

- 5 Uppfinningen avser vidare ett implantat för implantation i människor eller djur vilket implantat innefattar en linjär blockpolymer enligt uppfinningen.

#### UTFÖRINGSEXEMPEL

10

Exempel 1: 200 g (0,8 mol) 4,4'-difenylmetandiisocyanat (MDI) vägdes in i en flänskolv. Kvävgas lades på och MDI:n smältes långsamt vid 50°C. 202 g (0,38 mol). Polykaprolaktondiol (PCL) vägdes in i en dropptratt och tillsattes droppvis till den smälta MDI:n under långsam omrörning, T= 50-60°C.

15

24,6 g av den erhållna prepolymeren löstes upp under kvävgas i ca 127,6 ml dimetylformamid (DMF). 1,84 g (24,8 mmol) 1,3- diaminopropan och 0,13 g. (1,0 mmol) diaminobutan vägdes upp i en bägare och tillsattes tillsammans med 38,3 ml DMF till den upplösta prepolymeren under kraftig omrörning. En klar viskös lösning erhöles inom några sekunder.  $M_{peak} = 102000$  g/mol relativt PEO i DMF+0.5% LiCl.

20

Exempel 2: En prepolymer tillverkades enligt exempel 1 men med förändringen att 1075,9 g (2,03 mol) PCL blandades med 1035,2g (4,14 mol) MDI. 20,34 g av den erhållna prepolymeren löstes upp under kvävgas i 84,3 ml dimetylformamid (DMF). I kedjeförlängningssteget användes 19,8 mmol 1,3- diaminopropan, 0,51 mmol diaminobutan och 21,1 ml DMF. En klar viskös lösning erhöles inom några sekunder.  $M_{peak} = 106000$  g/mol relativt PEO i DMF+0.5% LiCl.

25

30

Exempel 3: 23,94 g prepolymer från exempel 2 löstes upp i 101,7 ml DMF. I kedjeförlängningssteget användes 23,8 mmol 1,5- diaminopentan, 0,9 mmol

diaminobutan och 25,5 ml DMF. En klar viskös lösning erhöles inom några sekunder.  $M_{peak}=106000$  g/mol relativt PEO i DMF+0.5% LiCl.

Exempel 4: En prepolymer tillverkades enligt exempel 1 men med förändringen att 1048.7 g (1.98 mol) PCL blandades med (1041.2 g) 4.06 mol MDI. 18.96 g av den erhållna prepolymeren löstes upp under kvävgas i ca 68.2 ml dimetylformamid (DMF). I kedjeförlängningssteget användes 17.7 mmol 1,2- diaminopropan, 3.1 mmol diaminobutan och 29 ml. En klar viskös lösning erhöles inom några sekunder.  $M_{peak}=25000$  g/mol relativt PEO i DMF+0.5% LiCl.

Exempel 5: 27,18 g av den erhållna prepolymeren i exempel 1 löstes upp under kvävgas i 104 ml dimetylformamid (DMF) och 1.23g MDI tillsattes. I kedjeförlängningssteget användes 31.9 mmol 1,3- diaminopropan, 1.3 mmol diaminobutan och 44.6 ml DMF. En klar viskös lösning erhöles inom några sekunder.  $M_{peak}=86000$  g/mol relativt PEO i DMF+0.5% LiCl.

#### MOLEKYLVIKTSMÄTNING

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Molekylvikten på de genom exemplen framställda polymererna mättes genom Size Exclusion Chromatography (SEC) med hjälp av en Waters 2690 Separations Module försedd med Waters 996 Photodiode Array Detector och en Waters 2410 Refractive Index Detector. Två Styragelkolonner, HT6E och HT3, kördes i serie med en flödes hastighet på 1 ml/minut i dimetylformamid (DMF) innefattande 0,005 g LiCl/l. Retentionstiden omvandlades till medelmolmassa ( $M_{peak}$ ), med användande av polyetylenoxid som standard.

25

Andra möjliga beredningsformer för den linjära blockpolymeren är exempelvis porösa filmer eller porösa polymermaterial.

30

Porösa filmer redogörs för i, t.ex. svenskt patent SE, C2, 514064, vilket här refereras till i sin helhet. Vidare beskrivs porösa polymermaterial exempelvis i svensk patentansökan SE, A, 0004856-1, vilken här refereras till i sin helhet. SE, A, 0004856-1 beskriver bland annat förfarande för framställning av ett

5 öppet poröst polymermaterial.

## FIBERSPINNING

- 10 I korthet tillgår fiberspinningsprocessen så att polymerlösningen extruderas genom en spinneret och ut i ett koaguleringsbad innehållande varmt vatten. I ett andra vattenbad sträcks fibern. Fibern rullas upp på en spole som sedan får torka.

## MEKANISKA EGENSKAPER HOS FIBERN

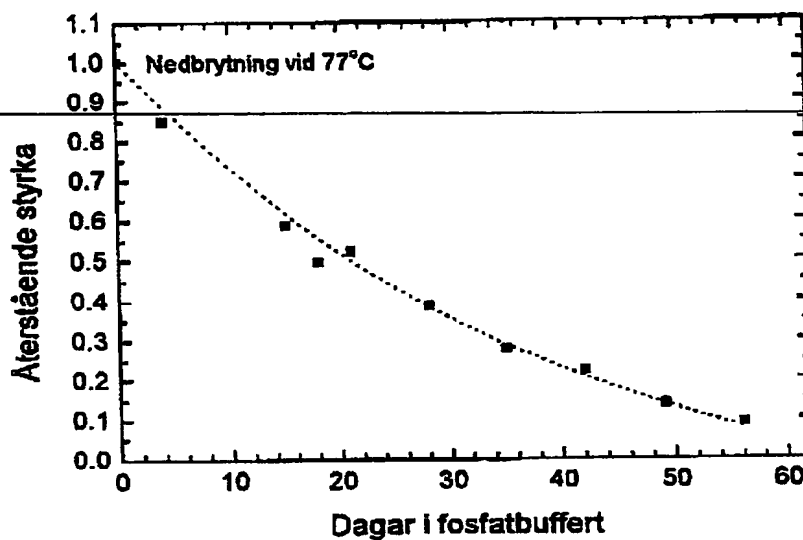
- 15 Denna spunna fibern testades med avseende på mekaniska egenskaper. Dessa resultat visas i tabellen nedan.

| Polymer.  | Spinningslös<br>ningsmedel | Specifik<br>(N/tex) | styrka | Styvhet x 10 <sup>3</sup> (N/mm) | Brottstjning<br>(%) |
|-----------|----------------------------|---------------------|--------|----------------------------------|---------------------|
| Exempel 1 | DMF                        | 0.25 ± 0.015        |        | 50 ± 3                           | 29 ± 4              |
| Exempel 2 | DMF                        | 0.28 ± 0.01         |        | 62 ± 4                           | 40 ± 3              |
| Exempel 3 | DMF+LiCl                   | 0.16 ± 0.015        |        | 56 ± 3                           | 28 ± 10             |



**NEDBRYTNINGSFÖRSÖK**

- En kontrollerad nedbrytning av polymeren i en takt som möjliggör reparation och/eller inväxt av kroppsegen vävnad är viktigt. Nedbrytningsförhållandena för den linjära blockpolymeren enligt uppfinningen studerades enligt följande.
- 5 Polymeren tilläts brytas ned i ett stort överskott av buffrad fosfatlösning med ett pH på 7.4. Temperaturen hölls vid 77 °C. Under tiden studerades bl.a. de mekaniska egenskaperna hos polymeren.



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**YTTERLIGARE ÅSKÄDLIGGÖRANDE AV UPPFINNINGENS UTFÖRANDE**

- In the present study we describe the synthesis, wet spinning, mechanical testing and degradation of poly(urethane urea)s (PUUR) intended for clinical use in anterior cruciate ligament (ACL) reconstruction. The effects of soft segment chemical composition and molar mass, and the kind of diamine chain extender on the material
- 15 properties were investigated. It was found that the fibres made of PUUR with

polycaprolactone diol (PCL530) as soft segment and MDI/1,3-DAP as hard segment, (PCL530-3), have high tensile strength and high modulus, and when degraded keep their tensile strength for the time demanded for the application. In conclusion, from a chemical and mechanical point of view PUUR fibres of PCL530-3, ARTELONTM, are suitable for designing a degradable ACL device.

### Introduction

Ligament injuries in the knee joint are among the most common sporting injuries.<sup>1,2</sup> Ruptures of the anterior cruciate ligament (ACL), the primary and most important stabiliser of the knee,<sup>3</sup> are the most common serious ligament injuries. In the 1960s the first ACL reconstructions with synthetic materials were performed.<sup>4</sup> The introduction of ligament prostheses generated much interest because it offered the benefit of quick recovery and rapid rehabilitation.<sup>5</sup> While early results were promising, the long-term results were disappointing. A number of problems were reported, including irreversible elongation, rupture and formation of wear debris.

Materials used for these prosthetic devices or reinforcement ligament bands were e.g. poly(tetrafluoroethylene), poly(ethylene terephthalate),<sup>1,4,6-9</sup> polypropylene, polyethylene, carbon fibres<sup>10</sup> and polydioxanone.<sup>11</sup> The common properties of these materials are a too high elastic modulus compared to native ACL and permanent deformation after repeated loading due to non-elastic behaviour.

Materials with elastic behaviour and modulus above rubber level can be found among the multiblock copolymers. Poly(urethane urea)s (PUUR) are multiblock copolymers, which combine excellent mechanical properties with documented blood

compatibility.<sup>12,13</sup> These properties have favoured the use and development of PUUR as biomaterials, particularly as products for blood applications.<sup>14-17</sup>

5 PUURs are made of soft segments based on polyether or polyester and hard segments based on the reaction of diisocyanate and diamine chain extender. Due to the thermodynamic incompatibility between the two segments, PUURs undergo micro-phase separation resulting in the phase-separated heterogeneous structure that can be considered as hard segment domains dispersed in a soft segment matrix. The various physical properties of the material such as strength, modulus, and elasticity are closely correlated with the domain structure and the interaction between the  
10 segments inside the domain. By adjusting the chemical nature and respective amounts of reagents, it is possible to obtain a wide range of materials with different properties. Thus, materials may be tailored for various applications.

In designing a degradable device for anterior cruciate ligament (ACL) reconstruction, whether a true prosthesis or an augmentation device, many biological  
15 and mechanical criteria must be met. High initial strength is needed to prevent mechanical failure of the implant prior to tissue ingrowth.<sup>18</sup> In addition, a moderate degradation rate is required to induce ingrowth of organized tissue.<sup>19</sup> If degradation is too rapid, the host tissue may be exposed to stresses that are too great, resulting in failure. On the other hand, if the degradation is too slow, stress shielding may  
20 occur.<sup>19</sup> Thus, a new material for ACL reconstruction should be 1) Compatible with surrounding tissues and allow cell ingrowth 2) Intended to be mechanically similar to native ACL 3) Degradable, but keeping at least 50% of its strength and stiffness for at least 9-12 months. A possible way to fulfil these requirements is to use a textile composition made of degradable PUUR fibres. Thus, the aim was to make PUUR

fibres suitable for designing a degradable ACL device. Previously made PUUR fibres of the Spandex type, e.g. Lycra, are unsatisfactory for use as ligaments. In particular, their elastic modulus is too low and they are not degradable.

In this paper the synthesis, wet spinning, mechanical properties and degradation of a number of PUUR fibres are presented. The effects of soft segment chemical composition and content and the kind of diamine chain extender on the material properties are investigated.

### Experimental section

**Materials.** Polycaprolactone diols (PCL) ( $\bar{M}_n = 530$  g/mol) and ( $\bar{M}_n = 1250$ , 2000 g/mol) were obtained from Solvay and Aldrich, respectively. Adipic acid, di(ethylene glycol), di-n-butylamine, ethylene diamine (EDA), 1,2-diaminopropane (1,2-DAP), 1,3-diaminopropane (1,3-DAP), 1,4-diaminobutane (1,4-DAB), 1,5-diaminopentane (1,5-DAPe), 1,6-diaminohexane (1,6-DAH) and lithium chloride (LiCl) were purchased from Fluka. 4, 4'-diphenylmethane diisocyanate (MDI) was provided by Bayer AB. N, N-dimethylformamide (DMF) 99.8% and toluene 99.8% were obtained from Labscan.

**Polyester synthesis.** Hydroxytelechelic polyesters were synthesized from adipic acid and di(ethylene glycol) with acid catalyst until the acid number was  $< 2$  as determined by titration of aliquots with 0.1 molar KOH in ethanol. The removal of water to drive the reaction at a reasonable rate was achieved by azeotropic distillation with toluene. Three products with hydroxyl numbers of 56 ( $\bar{M}_n = 2000$  g/mol), 112 ( $\bar{M}_n = 1000$  g/mol) and 223 ( $\bar{M}_n = 500$  g/mol), respectively, as determined according to ASTM D 4274-94, were used in the present study.

**Polymerization.** PUURs<sup>20</sup> were synthesized by a two-step method described earlier.<sup>21</sup> In the first step a prepolymer was formed. The polyester diol was added slowly to 4, 4'-diphenylmethane diisocyanate (MDI) (NCO: OH=2.05:1) in bulk at 50°C in a dry N<sub>2</sub> atmosphere. The isocyanate content was determined by reacting the prepolymer with an excess of di-n-butylamine in toluene. After the reaction was complete, the excess di-n-butylamine was determined by back titration with standard hydrochloric acid.

In the second step a dilute solution of diamine chain extender and monoamine chain stopper in DMF was added rapidly to a solution of prepolymer in DMF (20 wt.-%) under intense stirring at 20°C. The molar ratio NCO:NH<sub>2</sub> was 1:1 with 2% monoamine. The final polymer content was 18 wt.-%. The chemical compositions of the various PUUR can be seen in Table 1.

**Fibre spinning.** Fibres were prepared by a wet spinning process<sup>21</sup> (equipment from Bradford University Research Limited, Bradford, England). The polymer solution was metered through a spinneret (120 holes, Ø 80 µm) submersed in a coagulating bath containing water. In a second water bath the fibre bundle was drawn after which the multifilament fibre was taken up on a spool. The temperature in the water baths was varied from 20 to 80°C to get as high draw ratio as possible. The spools with fibres were rinsed in running tap water overnight and dried at room temperature. For each batch of fibres linear density, tensile strength, stiffness and elongation at break were determined.

**Band production.** The wet spun multifilament fibres were by doubling and slight twisting converted to a coarse yarn, which was used as warp threads. The bands were woven on a narrow fabric needle loom (type FX2/65, Mageba Textilmaschinen

Vertriebs GMBH, Germany) with low weft tension in plain weave to utilise as much as possible of the yarn strength combined with good stability.

**Density measurements.** The density of the fibres was measured with a Micrometrics Multivolume Pycnometer 1305.

- 5 **Porosity measurements.** Pore sizes and pore size distributions of the woven bands were measured by mercury porosimetry, Micromeritics AutoPore III 9410.

**Polymer degradation.** Samples of fibres and bands were placed in vials in a great surplus of 0.06 M phosphate buffer solution pH 7.4 ( $\text{Na}_2\text{HPO}_4$  and  $\text{KH}_2\text{PO}_4$ ).<sup>22</sup> The sealed vials were placed in thermostat ovens at 37°C and 77°C. At intervals the vials  
10 were opened and aliquots of material were taken out. Changes in molar mass and loss of tensile strength were investigated.

**Size Exclusion Chromatography (SEC).** Size Exclusion Chromatography (SEC) was conducted with a Waters 2690 Separations Module equipped with a Waters 996 Photodiode Array Detector and a Waters 2410 Refractive Index Detector. Two  
15 Styragel columns, HT6E and HT3, were operated in series at a flow rate of 1 ml/min in DMF containing 0.5%(w/v) LiCl to prevent aggregation. The retention times were converted to apparent molar masses using poly(ethylene oxide) standards.

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**Linear density measurements.** The linear density of the fibres was determined by weighing of a known length of fibre, typical 100 m, and is presented in tex. The tex  
20 unit is defined as g/ 1000 m.

**Mechanical testing.** After equilibration with water at 20°C for 30 minutes, the multifilament fibres and the woven bands were tested in the wet state in a tensile tester (UT 350/5 LS Universal Testing machine SDL International Ltd. Stockport).

The constant rate of extension was 900 mm/minute and the sample lengths were 100 mm for fibres and 30 mm for the woven bands.

**Differential Scanning Calorimetry (DSC).** Thermal analysis was carried out on a Perkin-Elmer Pyris1. The heating rate was 10°C /min over a temperature range of –  
5 100 to 150°C. The sample was cooled to -100°C and then a second run was performed. Glass transition temperatures were determined from the second scan.

### Results and Discussion

**Polymerization.** In a first study, PUURs were synthesized using poly(di(ethylene glycol) adipate) (PDEA) or polycaprolactone diol (PCL), with different molar masses  
10 as soft segments, MDI and EDA as chain extender (Table 1). The length of the soft segment was altered by changing the molar mass of the polyesterdiol while the length of the hard block was unchanged. However, there was a distribution of hard block lengths as a consequence of the stoichiometric ratio in the prepolymerization step.<sup>23</sup> As the soft segment was shortened from 2000 g/mol to 500 g/mol the hard  
15 block content increased from 23 % by weight to 55%. An immediate effect was that the solubility in DMF decreased with increasing hard block content, resulting in turbidity and gelation a few minutes after chain extension.

Another series of PUURs was prepared using PCL530 as soft segment, MDI and six different aliphatic diamines as chain extenders (Table 1).

**Table 1. Composition and solubility of PUURs.**

| Sample code | Chain extender | Soft segment $\bar{M}_n$ | Hard block content (%) | DMF solution (18%, 22°C) | $M_{peak} \times 10^{-3}$ |
|-------------|----------------|--------------------------|------------------------|--------------------------|---------------------------|
| PDEA2000-2  | EDA            | 2000                     | 23.0                   | Opaque <sup>a</sup>      | 86                        |
| PDEA1000-2  | EDA            | 1000                     | 37.7                   | Opaque                   | 86                        |
| PDEA500-2   | EDA            | 500                      | 55.9                   | Opaque                   | 115                       |
| PCL2000-2   | EDA            | 2000                     | 23.0                   | Opaque                   | 105                       |
| PCL1250-2   | EDA            | 1250                     | 33.0                   | Opaque                   | 121                       |
| PCL530-2    | EDA            | 530                      | 51.4                   | Opaque                   | 125                       |
| PCL530-2Me  | 1,2-DAP        | 530                      | 52.0                   | Clear <sup>b</sup>       | 106                       |
| PCL530-3    | 1,3-DAP        | 530                      | 52.0                   | Clear                    | 125                       |
| PCL530-4    | 1,4-DAB        | 530                      | 53.0                   | Opaque                   | 123                       |
| PCL530-5    | 1,5-DAPe       | 530                      | 53.6                   | Opaque                   | 106                       |
| PCL530-6    | 1,6-DAH        | 530                      | 54.2                   | Opaque                   | 106                       |

a) Opaque: hazy, poorly solubilized in the above condition.

b) Clear: transparent, absolutely solubilized in the above condition.

c) Poly(ethylene oxide) equivalent  $M_{peak}$ .

- 5 The different chain extender structures affected the solubility of the polymer in DMF. These PUURs have almost the same hard/soft ratio and showed solubility in the order 1,2-DAP>1,3-DAP>1,5-DAPe>1,6-DAH>1,4-DAB>EDA. In the reactions all diamines but 1,2- and 1,3-DAP gave rise to turbid solutions 5-20 minutes after chain extension. After still some time brittle gels were formed. 1,3-DAP formed clear
- 10 polymer solutions, but they were turbid and gelled after a few days. PCL530-2Me solutions remained clear for at least one year. This is the most apparent difference



between 1,2-DAP and the other five chain extenders and is explained in terms of less efficient hydrogen bonding due to steric effects from the pendant methyl group. Similar behaviour has been seen for PUUR systems chain extended with aromatic diamines with substituents that increased the steric effects.<sup>24</sup>

- 5     The lower solubilities of the other PUURs probably depend on the influence of the urea structure on the association behaviour. PUUR solutions with even number of methylene groups in the chain extender got turbid very soon while odd numbered remained clear for longer times. Similar results were found by Joel et al.,<sup>25</sup> who studied steric odd-even effects of various urea structures of PUUR on solution
- 10   properties in DMF. They found that the viscosity of solutions with odd number of methylene groups was independent of time, while the even numbered ones showed turbidity and a drastic increase in viscosity with time followed by gelation. The turbidity was explained by formation of a higher concentration of physical crosslinks caused by hydrogen bonding within the hard block domains.<sup>26</sup> The solution process
- 15   becomes restricted if the hard segment domains are perfectly arranged and form a physically crosslinked network. Thus, the good solubility of PCL530-3 may be explained by a lower degree of hydrogen bonding compared to the other chain extenders.

- 20   A requirement for spinnability is that the polymer is soluble. The solvent, DMF, should prevent gelation due to hard segment interaction before spinning, but the solubility of PUUR in DMF is poor. By adding LiCl (0.07 g LiCl /g polymer solution) to the polymer solutions turbidity could be removed and gelation could be prevented.<sup>25</sup> The increased solubility is based on the destruction of the hydrogen

bonds between chains and on a simultaneous blocking of the acceptor positions owing to the favoured complex formation between Li and carbonyl oxygen.<sup>27</sup>

**Fibre spinning.** The fibres are formed in a wet spinning process. In the first step precipitation occurs and the solvent diffuses out of the extrudate into the bath, and  
5 non-solvent diffuses from the bath into the extrudate. The rate of the coagulation has a profound effect on the yarn properties. Important process variables are for example concentration and temperature of the spinning solution, composition and temperature of the coagulation bath.

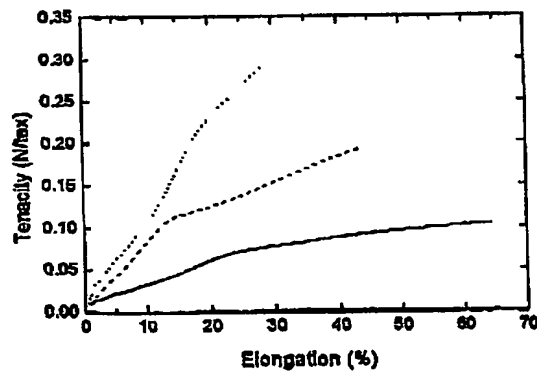
The temperature of the spinning solutions was kept within 20-25°C and the  
10 polymer concentration was 18 wt.-%. No correlation between polymer content and tensile properties could be seen. However, a spinning solution viscosity of more than 1 Pas was needed to be able to get a stable spinning process.

The temperature of the coagulation bath was found to be of great importance. The rate of PUUR coagulation occurring when the polymer solution was extruded into  
15 the water depends on the coagulation temperature and influences both the morphology of the undrawn fibre and the ultimate fibre properties. The suitable spin bath temperature for PDEA based PUURs was about 20°C (Table 2). At higher temperatures the polymer got stuck in the spinneret. In contrast the PCL based PUURs seemed to be easier to spin the higher the temperature (Table 2). This  
20 difference between the two polyesters can be due to their difference in hydrophilicity

<sup>28</sup>

In the second water bath the fibre bundle is drawn to get molecular chain orientation and thereby improve the mechanical properties. The higher the draw ratio, the lower the elongation and the stiffer and stronger the fibre.

The effect of draw ratio on tensile properties for PCL530-3 is seen in Figure 1.



**Figure 1. Tensile test diagrams for PUUR fibre of PCL530-3 showing changes produced by increasing orientation and improving structure. Draw ratio — 3.5, -- 3.8**

5 and ---- 5.4.

Table 2. Spin parameters for different PUURs

| Sample code | Spin solvent | $T_{\text{draw optimal}}^a$<br>(°C) | Draw ratio <sub>20°C</sub> /<br>Draw ratio <sub><math>T_{\text{draw optimal}}</math></sub> | Draw ratio |
|-------------|--------------|-------------------------------------|--|------------|
| PDEA2000-2  | DMF+LiCl     | 20                                  | -  | 5          |
| PDEA1000-2  | DMF+LiCl     | 20                                  | -  | 5          |
| PDEA500-2   | DMF+LiCl     | 20                                  | -  | 4.5        |
| PCL2000-2   | DMF+LiCl     | 60                                  | 0.58   | 6          |
| PCL1250-2   | DMF+LiCl     | 60                                  | 0.57   | 6          |
| PCL530-2    | DMF+LiCl     | 60                                  | 0.72   | 5          |
| PCL530-2Me  | DMF          | 60                                  | 0.67   | 9          |
| PCL530-3    | DMF          | 60                                  | 0.72   | 5.4        |
| PCL530-3    | DMF+LiCl     | 80                                  | 0.44   | 5.4        |
| PCL530-4    | DMF+LiCl     | 80                                  | 0.70   | 5.4        |
| PCL530-5    | DMF+LiCl     | 80                                  | 0.46   | 6.4        |
| PCL530-6    | DMF+LiCl     | 80                                  | 0.54   | 7.4        |

a)  $T_{\text{draw optimal}}$  = the temperature at which the highest draw ratio is achieved

The draw ratio of the fibres is dependent on the temperature not only in the coagulation bath but also in the stretching bath. It was found that the best processability and draw ratio were achieved when the baths had the same temperature. The spinning conditions are shown in Table 2. Three different groups are identified. The first group contains PDEA based PUURs, described earlier, which have best processability and draw ratio at 20°C. The second group contains PCL based PUURs chain extended with EDA spun from DMF+LiCl, and PCL530-2 Me

(b)

**Figure 2.** Draw ratio<sub>20°C</sub>/Draw ratio<sub>T<sub>c</sub></sub>; a) (■) PCL530-3 and (●) PCL530-5; b) (▲) PCL530-4 and (◆) PCL530-6.

The increase in draw ratio of PCL530-5 was almost proportional to the temperature, while the increase in draw ratio of PCL530-3 showed weak temperature dependence between 20°C and 50°C. Above that interval the drawability was directly proportional to the temperature. The drawability of PCL530-4 and PCL530-6 was constant at temperatures below 60°C and 70°C, respectively. At these temperatures strong temperature dependence in drawability appeared. Additional investigations are needed to explain these differences.

**Band production.** The appropriate force at break of the finished and sterilised band should be 1200 N. Based on practical experiences the theoretical breaking force therefore was chosen to 1600 N in order to calculate the resulting cross section of the band as well as the number of fibres needed. Furthermore the diameter of the band was not allowed to exceed  $5 \pm 1$  mm. In the finished band three circular yarns are placed in a triangular form. Assuming hexagonal close packing of the fibres in the yarn,<sup>29</sup> the yarn radius can be calculated. From the calculations it is given that the tenacity of the fibres should be at least 0.2 N/tex to meet the criteria of strength and size.

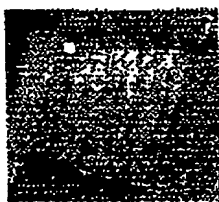
**Porosity measurements.** In medical applications the pore sizes and their distributions are of great importance for promoting cell ingrowth. The multifilament fibres made from wet spinning have a high void content. Furthermore, when fibres are processed into woven structures, varying degrees of porosity can be provided. The pore sizes and pore size distribution of two woven bands made of 1500

multifilament PCL530-3 fibres are presented in Table 3. The smallest pores,  $<8 \mu\text{m}$ , is probably between the filaments in the multifilament fibre while pores between  $8 \mu\text{m}$  and  $600 \mu\text{m}$  is the space between the fibres in the warp and weft (Figure 3). Almost half of pores (49%) are  $21\text{--}100 \mu\text{m}$ , sizes that may be suitable for fibrous connective tissue ingrowth.<sup>30</sup> About 20% of the pores are  $100\text{--}400 \mu\text{m}$ , pore sizes, which have been shown to be suitable for osteoblast ingrowth in hard tissue applications.<sup>31</sup>

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**Table 3. Pore sizes and pore size distributions of PUUR bands.**

| Interval ( $\mu\text{m}$ ) | Pores (%) |
|----------------------------|-----------|
| 401-600                    | 6.8       |
| 201-400                    | 15.6      |
| 101-200                    | 8.0       |
| 51-100                     | 20.7      |
| 21-50                      | 28.3      |
| 8-20                       | 10.7      |
| 1.0-7.9                    | 4.5       |
| <1                         | 5.4       |



(a)



(b)

**Figure 3. SEM micrographs of the surface of a) wet spun and woven PUUR fibre**  
5 bar=50  $\mu\text{m}$ ; b) wet spun PUUR fibre bar=5  $\mu\text{m}$ .

**Mechanical testing.** The tensile properties of the fibres are shown in Table 4. In the first series the length and composition of the esterdiol was varied and the hard



block was formed from MDI and EDA. The effects upon shortening the soft segment were seen in increased stiffness and decreased elongation of the fibres. The largest effect is seen when comparing polymers made from soft segments of molar masses of ~1000 g/mol and ~500 g/mol. As a consequence of the shortening of the soft segment the hard/ soft ratio increases. The hard blocks, which are extensively hydrogen bonded, mainly affect the stiffness and serve as both cross-links and filler particles in the soft segment matrix. It is known that the strength and modulus of polyurethane copolymers are directly related to the amount and stability of the hard segment domains.<sup>32</sup> Wang and Cooper<sup>32</sup> studied the effect of the hard block content and block length on the morphology and properties of PUURs systematically. They found that the mechanical properties depended primarily on the hard block content and the strong hard-domain cohesion due to interurea hydrogen bonding that resulted in semicrystalline behaviour.

The effects on the mechanical properties of the PCL 530 based PUUR fibres chain extended with six different aliphatic diamines were investigated (Table 4). The hard segment content is almost constant, but their structures differ. The strongest fibres were obtained from PCL530-2Me and PCL530-3, which are supposed to be less efficiently hydrogen bonded in solution compared to the other PUURs. PCL530-2Me and PCL530-3 formed clear solutions and could be spun without addition of LiCl. As LiCl was added to a PCL530-3 solution the tenacity of the fibre produced thereof decreased more than 40%. Nevertheless, the tenacity of PCL530-3 fibre from DMF+LiCl was still among the highest. Upon a comparison of fibres spun from DMF-LiCl solutions PCL530-3 and PCL530-5 are the strongest. Thus, chain extenders with an odd number of methylene groups tend to form stronger fibres than



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**Table 4. Mechanical properties of different PUUR fibres.**

| Sample code | Spin solvent | Tenacity (N/tex) <sup>a</sup> | Stiffness x 10 <sup>3</sup> (N/mm) | Elongation at break (%) |
|-------------|--------------|-------------------------------|------------------------------------|-------------------------|
| PDEA2000-2  | DMF          | 0.06 ± 0.004                  | 6 ± 0.5                            | 130 ± 13                |
| PDEA1000-2  | DMF          | 0.06 ± 0.004                  | 6 ± 0.4                            | 120 ± 10                |
| PDEA500-2   | DMF+LiCl     | 0.08 ± 0.005                  | 17 ± 1                             | 50 ± 5                  |
| PCL2000-2   | DMF+LiCl     | 0.13 ± 0.007                  | 6 ± 0.3                            | 77 ± 12                 |
| PCL1250-2   | DMF+LiCl     | 0.11 ± 0.005                  | 6 ± 0.4                            | 74 ± 14                 |
| PCL530-2    | DMF+LiCl     | 0.10 ± 0.01                   | 45 ± 2                             | 32 ± 8                  |
| PCL530-2Me  | DMF          | 0.25 ± 0.015                  | 50 ± 3                             | 29 ± 4                  |
| PCL530-3    | DMF          | 0.28 ± 0.01                   | 62 ± 4                             | 40 ± 3                  |
| PCL530-3    | DMF+LiCl     | 0.16 ± 0.008                  | 50 ± 3                             | 34 ± 2                  |
| PCL530-4    | DMF+LiCl     | 0.10 ± 0.01                   | 60 ± 3                             | 25 ± 3                  |
| PCL530-5    | DMF+LiCl     | 0.16 ± 0.015                  | 56 ± 3                             | 28 ± 10                 |
| PCL530-6    | DMF+LiCl     | 0.11 ± 0.01                   | 70 ± 3                             | 16 ± 5                  |

<sup>a</sup>) Density of fibres = 1.23 g/cm<sup>3</sup>

**Bands.** Typical tensile test diagram of a band of PCL 530-3 fibres is given in Figure 4. The shape of load-elongation curve of the band is similar to that of the fibre, but the elongation is higher. This is expected as the fibres are slightly twisted to get a coarse yarn before weaving.

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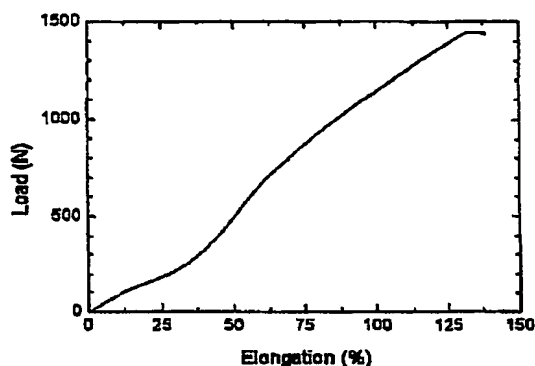


Figure 4. Typical tensile test diagrams for a PUUR band of PCL530-3 fibres.

**Differential Scanning Calorimetry.** The glass transition temperatures of the soft blocks for the different PUURs are presented in Table 5. As the molar mass of the soft segments decreased the  $T_g$  increased from  $-30.7$  to  $-5.5^\circ\text{C}$  and from  $-48.3$  to  $-11.3^\circ\text{C}$  for PDEA and PCL respectively. The  $T_g$  was harder to detect the shorter the soft segment. The effect of soft segment length on its  $T_g$  is related to the limitation of the soft segment mobility imposed by the attached hard segment. Beside the molar mass of the soft segment, the chain extender affected the  $T_g$  so some extent. PCL530-2Me and PCL530-3 showed the highest  $T_g$ . For chain extenders with three or more methylene groups there was a movement towards higher  $T_g$  the longer the diamine. All PUUR fibres but PCL530-2Me and PCL530-3 were spun from DMF+LiCl. PCL530-3 spun from DMF+LiCl showed no change in  $T_g$  compared to PCL530-3 spun from DMF. The phase mixing of soft and hard segments makes thermal molecular motion in soft segment phase restricted. Therefore, the shifts of  $T_g$  to higher temperatures are attributed to the interaction between hard and soft segments.

Table 5. DSC data

| Sample code     | Soft segment |
|-----------------|--------------|
|                 | $T_g$ (°C)   |
| PDEA2000-2      | -30.7        |
| PDEA1000-2      | -25.7        |
| PDEA500-2       | -5.5         |
| PCL2000-2       | -48.2        |
| PCL1250-2       | -39.1        |
| PCL530-2        | -11.3        |
| PCL530-2Me      | -9.2         |
| PCL530-3        | -8.4         |
| PCL530-3 (LiCl) | -8.3         |
| PCL530-4        | -10.2        |
| PCL530-5        | -11.2        |
| PCL530-6        | -13.7        |

**Degradation studies.** Among the various bonds present in PUUR, the most susceptible ones are the ester bonds of the soft segments which upon hydrolysis yield

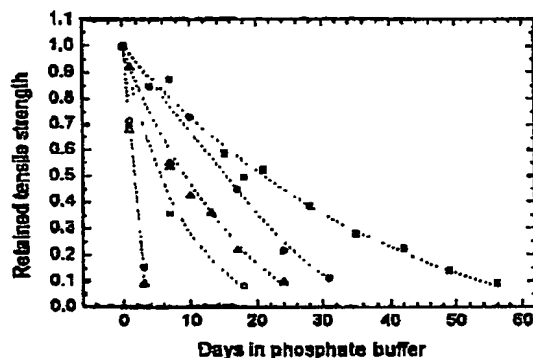
5 carboxylate and hydroxyl groups. The acid produced can catalyse the ester hydrolysis so that an autocatalytic reaction becomes prevalent. Furthermore, the intended use for the material is in the knee that has a neutral pH.<sup>33</sup> For that reason all degradation studies were carried out in a great surplus of buffered solutions at pH

7.4. Both changes in molar mass and tensile strength of optimal drawn fibres and

10 bands thereof were studied. The data for fibres and bands obey the same dependence

on change in molar mass and tensile strength. Thus, the difference in fibre packing and sample thickness do not seem to have any effect on degradation rate.

The loss in tensile strength with hydrolysis time at 77°C is shown in Figure 5.



5

**Figure 5. Tensile strength retention as a function of hydrolysis time of different PUURs at 77°C (■) PCL530-2 and PCL530-3, (●) PCL1250-2, (▲) PCL2000-2, (□) PDEA500-2, (○) PDEA1000-2, (△) PDEA2000-2.**

For both PDEA- and PCL-based PUUR the polymer with longer soft segments degraded faster. Thus, PDEA2000 and PCL2000 display lower hydrolytically stability than PCL530 and PDEA500, respectively. The reason is a higher fraction of soft segments and, consequently, of ester groups exposed to hydrolysis.

The chemical composition of the ester affects the degradation rate of the different PUURs. PUURs with soft segments made of PDEA degrade faster than those based on PCL. The superior resistance to hydrolysis is ascribed to the hydrophobicity of PCL. It has been shown that the introduction of hydrophilic poly(oxyethylene) blocks in PCL-POE-PCL triblock copolymers did increase the hydrophilicity and degradation rate compared with the homopolymer PCL<sup>28</sup>. PDEA 500 contains about

three diethylene glycols whereas the PCL diols initiated with diethylene glycol contain one.

The initial molar mass of the different PUURs varied to a small extent (Table 1). The rate of the decrease in tensile strength was not affected, but the time to complete degradation became somewhat shorter the lower the initial molar mass. The molar mass decreases after an induction period of about 10 days for PCL530-2 and-3 and about 3 days for PCL1250-2 (Figure 6). No induction period was seen for the other samples. During the induction period a decrease in SEC retention time was seen. The phenomenon has been occasionally reported by some researchers using both *in vitro* and *in vivo* systems,<sup>34-36</sup> but no unanimous conclusions on the reasons for the increase were drawn. We have interpreted the decrease in retention time, as aggregation of the polymer due to a physical process since no unreacted isocyanate groups is present in the polymers. Furthermore, in spite of the increase in molecular size the tensile strength decreased already after 2 days in phosphate buffer (Figure 5).

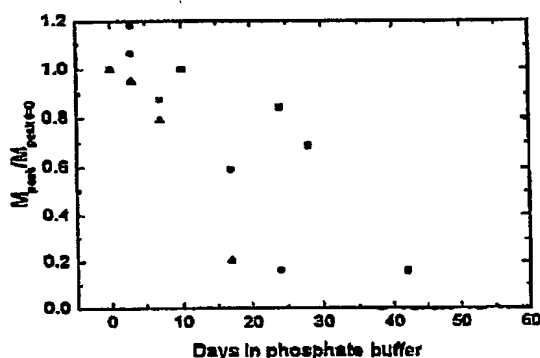


Figure 6. Molar mass as a function of hydrolysis time of different PCL based PUURs at 77°C (■) PCL530-3, (●) PCL1250-2, (▲) PCL2000-2.

One of the requirements of the material was that at least 50 % of the tensile strength should be kept for at least 9-12 months. For use at body temperature it is interesting to estimate and investigate the conformity between the degradation rate at 37°C and 77°C.

- 5 Since fibres of PCL530-3 seem to have the most promising properties from many aspects further degradation studies at 37°C were made these fibres. The change in molar mass at 37°C follows the same pattern as at 77°C. After about 40 days a decrease in SEC retention time for the polymer is seen, which is similar to the results after 2-3 days at 77°C. After that the retention time is constant for a long period of
- 10 time. This means that the size of the formed aggregates is to some extent independent of the molar mass of the molecules that take part in the aggregate formation. It is obvious that the degradation proceeds since after 500 days the SEC retention time has increased accompanied by a the loss in tensile strength of 5-10%. Thus, the degradation rate at 37°C seems to be about 1/20 lower than of the degradation rate at
- 15 77°C.

- In addition to loss of tensile strength and molar mass, the mass change of the PCL530-3 fibres has been studied. First the mass of the fibres increased about 8-10% due to water adsorption. After 52 days at 77°C there were signs of mass loss and after another ten days the mass loss is obvious (-30%). At that time the fibres were
- 20 very brittle at and further measurements were hard to perform. In accordance with the low degradation rate at 37°C it is not expected to see any decrease in the mass before 800-850 days of degradation.



Regarding the biocompatibility of the PCL530-3 both safety studies, mutagenicity and delayed contact hypersensitivity, and implantation studies have been performed and reported.<sup>37</sup> When PUUR bands made of PCL530-3 fibres were used as ACL prosthesis in rabbits and minipigs, bone formation was seen in the drilled tunnels and surrounding the PUUR fibres. Also, irrespective of observation time, connective tissue in growth was observed between and in close contact with the PUUR fibres in both species. At observation times exceeding 6 months, the connective tissue had an orientation of the collagen fibres and fibroblasts in parallel with the PUUR fibers.<sup>37</sup> From clinical trials using the PUUR band as an ACL augmentation, biopsies were obtained from 5 patients at times between 30 to 40 months. As in the animals a high percentage of connective tissue ingrowth was found in close contact with the material and the presence of collagen type I and blood vessels was confirmed using immunohistochemical methods. No indications of obvious inflammatory reaction or foreign body response were detected.

**Conclusions.** We have demonstrated that the chemical composition of PUUR can be tailored to get fibres with strength, stiffness and degradation rate, which fulfil the desired properties of a material for ACL reconstruction.

Fibres made of PUUR based on PCL 530 have superior strength and stiffness compared to other polyesterdiols used in the study and keep at least 50 per cent of its original tensile strength more than nine months at body temperature. Furthermore, chain extension of PCL530:MDI with 1,3-DAP produces a polymer solution from which strong fibres can be spun without additives. A porous band with appropriate strength and size can be woven of the fibres.

In conclusion, from a chemical and mechanical point of view fibres of PCL530-3, ARTELON™, are suitable for designing a degradable ACL device. Human clinical trials with ACL reconstruction using the PUUR band are in progress.

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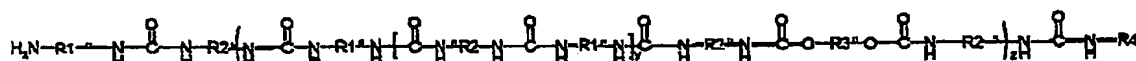
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## PATENTKRAV

1. Linjär blockpolymer vilken beskrivs enligt formeln:

5



10 varvid

**R1 är härledd från en diamin, t.ex. etylendiamin, 1,2-diaminopropan eller 1,3-diaminopropan;**

15 R2 är härledd från 4,4'-difenylmetandiisocyanat, 4, 4'-cyklohexylmetandiisocyanat, hexametylendiisocyanat, etyl-2,6-diisocyanathexanoat, isofomdiisocyanat, eller 1,4 diisocyanatobutan ;

**R3 är härledd från en esterdiol:**

**R4 är härledd från dibutylamin eller etanolamin;**

20 där  $0 < y < 4$  och  $z > 8$ .

kännetecknad av

att de monomerer som R1 och R2 är härledda från tillsätts i sådana mängder  
25 att molförhållandet mellan R1 och R2 är större än 2:1.

2. Linjär blockpolymer enligt krav 1, varvid R1 är härledd från etylendiamin, 1,3- diaminopropan, 1,2- diaminopropan, 1,4- diaminobutan, 1,5- diaminopentan, eller 1,6 -diaminohexan.

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3. Linjär blockpolymer enligt krav 1 eller 2, varvid R3 är härledd från polykaprolaktondiol, polydietylenglykoladipat, eller poly(pentandiolpimelat).
- 5 4. Fiber framställd av en linjär blockpolymer enligt något av ovanstående krav.
5. Fiber enligt krav 4, vilken uppvisar en seghet på åtminstone 0.1 N/tex.
- 10 6. Fiber enligt krav 5, vilken uppvisar en seghet överstigande 0.2 N/tex.
7. Fiber framställd av en linjär blockpolymer enligt något av ovanstående krav, vilken uppvisar en brottöjning som understiger 100 %.
- 15 8. Film framställd av en linjär polymer enligt något av kraven 1-3.
9. Poröst polymermaterial framställd av en linjär polymer enligt något av kraven 1-3.
- 20 10. Implantat för implantation i människor eller djur vilket implantat innefattar en linjär blockpolymer enligt något av ovanstående krav.





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